Adrenal disorders in human immunodeficiency virus (HIV) infected patients

Altérations de la fonction surrenalienne chez les patients infectés par le virus de l’immunodéficience humaine (VIH)

Justine Bons¹,¹, Lucile Moreau¹,¹, Hervé Lefebvre²,³,*,

¹ Service d’endocrinologie, diabète et maladies métaboliques, CHU de Rouen, 1, rue de Germont, 76031 Rouen, France
² Inserm U982, université de Rouen, 76821 Mont-Saint-Aignan, France
³ Institut de recherche et d’innovation biomédicale, 76183 Rouen, France

Abstract

Human Immunodeficiency Virus (HIV) infection is associated with adrenal disorders, which must not be underestimated. Adrenal morphologic changes are primarily related to opportunistic infections, mostly by cytomegalovirus and mycobacteria, and malignant tumours such as non-Hodgkin’s lymphoma and Kaposi’s sarcoma. The most frequent biological alteration reported to date is the increases in cortisol concentrations which results from a decrease in cortisol metabolism and hyperactivity of the hypothalamo-pituitary-adrenal axis commonly referred to as pseudo-Cushing’s syndrome. These modifications can be a consequence of antiretroviral therapy and do not require any investigation or specific treatment. Conversely, adrenal insufficiency, either iatrogenic or secondary to glandular infiltration by neoplasms or infections, needs long-term substitution with hydrocortisone, but at present occurs more rarely and usually at late stages of disease progression. The impact of HIV infection on the other adrenocortical functions has been less reported in the literature although several studies show low levels of adrenal androgens, especially dehydroepiandrosteredione (DHEA). Impairment in mineralocorticoid function appears occasional and remains a subject of debate.

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Résumé

Les patients infectés par le virus de l’immunodéficience humaine (VIH) présentent des anomalies surrenaliennes à ne pas méconnaître. Les atteintes morphologiques de la surrenale sont principalement liées aux infections opportunistes, majoritairement par le cytomegalovirus et les mycobactéries, ainsi qu’aux tumeurs malignes telles que les lymphomes non hodgkiens et les sarcomes de Kaposi. Les anomalies biologiques les plus souvent observées correspondent à une élévation des taux de cortisol qui relève à la fois d’une réduction du métabolisme de ce dernier et d’une hyperactivité de l’axe corticotrope rentrant dans le cadre des pseudo-syndromes de Cushing. Ces modifications peuvent être liées au traitement antirétroviral et ne nécessitent aucune investigation ni particulier. À l’inverse, l’insuffisance surrenalienne, d’origine iatrogène ou secondaire à l’infiltration tumorale ou infectieuse, requiert une prise en charge au long cours, mais s’avère à l’heure actuelle rare et survient généralement à des stades plus avancés de la maladie. Le retentissement de l’infection à VIH sur les autres sécrétions corticosurrénales est moins connu. Néanmoins, les études s’accordent à montrer des taux abaissés d’androgènes surrenaliers, en particulier de déhydroépiandrosteredione (DHEA). L’atteinte de la fonction minéralocorticoïde reste peu fréquente et discutée.

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1. Introduction

With 7000 to 8000 new human immunodeficiency virus (HIV) infections per year in France according to the latest report by Professor Yeni in 2010 [1], the issue of the link between HIV and endocrine disorders is a real concern. In this article, we focus our discussion on the impact of HIV infection on the adrenal gland. At the onset of the acquired immune deficiency syndrome (AIDS) epidemic, the diverse adrenal manifestations of HIV were mainly a consequence of opportunistic infections (OIs) or malignant tumours. At present, the use of antiretroviral therapy has greatly reduced the incidence of adrenal gland infiltration due to tumour or infectious processes, but sometimes with significant iatrogenic consequences.
2. Adrenal incidentalomas

Adrenal masses of tumoural origin may be incidentally discovered or revealed by adrenal imaging during exploration for clinical symptoms. Malignant tumours are more often aggressive, primarily occur in young subjects and respond poorly to standard treatment [2].

The two causes of adrenal tumoural lesions, particularly observed in HIV patients, are Kaposi’s sarcoma, secondary to co-infection with the oncogenic human herpes virus type 8 (HHV8), and non-Hodgkin’s lymphoma of a high-grade malignant B phenotype, which can be promoted by the Epstein-Barr virus (EBV; [2-5]). The adrenal localization of Kaposi’s sarcoma is exceptionally isolated, and usually asymptomatic and often associated with other organ involvement (liver, spleen, lymph nodes, gastrointestinal tract, lungs) [6]. Non-Hodgkin’s lymphoma may be responsible for unilateral or bilateral adrenal lesions, which are round, 1.5 to 10 cm in diameter, hypodense, and slightly enhanced after contrast material injection [7].

Conversely, the other causes of adrenal masses reported in AIDS patients commonly occur in the general population, i.e. unilateral or bilateral metastases of the lung and breast carcinomas, adenocortical carcinomas [8], smooth muscle malignant tumours or leiomyosarcomas most often secondary to co-infection by EBV [9], angiosarcomas and rhabdomyosarcomas [10].

Benign adrenal tumours have also been reported, with no specific link to HIV. They most often appear as homogeneous and hypodense on CT scan. These adrenal masses include steroid-secreting adenomas responsible for Cushing’s syndrome or primary aldosteronism [11], pleomorphic adenomas [12], adenomatoid tumours derived from mesothelial cells [13] and adrenal leiomyomas [14-16].

Opportunistic infections can sometimes appear as bilateral adrenal incidentalomas and cause primary adrenal insufficiency via bilateral destruction of the glands.

The main cause of adrenal gland destruction is infection with cytomegalovirus (CMV), which occurs when the CD4 lymphocyte count is less than 50/mm³. In an autopsy series, 40-88% of patients presented with nuclear and cytoplasmic inclusions due to CMV in adrenal tissues. The histological appearance of the adrenal gland varies in this context from focal inflammation to extended bleeding areas that sometimes principally involve the medulla. However, the extent of adrenal necrosis induced by CMV does not usually exceed 60-70% of the total parenchyma and is therefore rarely responsible for adrenal insufficiency [17,18].

The other causes of bilateral adrenal infiltration, most often responsible for adrenal insufficiency, are bacterial infections with Mycobacterium tuberculosis [19], Mycobacterium avium intracellulare (MAI), Mycobacterium kansasii [20] and Nocardia, as well as fungal infections with Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis and Coccioidoides immitis and posadasi. These infections are most frequently found on CT scan and present as adrenal masses with central hypodensity and peripheral contrast enhancement [21].

Intra-adrenal parasitic locations are also possible. In fact, the presence of hydatid cysts in the adrenal gland has been described, most often in the context of disseminated infections caused by Echinococcus granulosus. These cysts are usually unilateral and asymptomatic, but may cause pain in cases of haemorrhage, rupture or infection [22]. The CT scan reveals a primarily cystic mass, sometimes associated with calcifications. Toxoplasma gondii and Pneumocystis carinii infections have also been shown to be present at the adrenal level [23,24].

The main aetiologies of adrenal lesions reported in HIV-positive patients as well as the biological explorations that should routinely be performed in case of discovery of these masses are summarized in Fig. 1.

3. HIV and glucocorticoids

3.1. Adrenal insufficiency

Although adrenal insufficiency is often subclinical and consequently under-diagnosed, its prevalence appears to be greater in patients with untreated HIV than in the general population. Moreover, it has been reported that up to 17% of hospitalized AIDS patients have an insufficient plasma cortisol response to Synacthen test. It is therefore recommended to screen for adrenal insufficiency in symptomatic HIV patients [25].

3.1.1. Peripheral adrenal insufficiency

Primary adrenal failure is rarely diagnosed because the symptoms do not appear until more than 80% of the adrenal glands have become necrotic. Overt adrenal insufficiency is therefore observed in advanced stages of HIV infection in only 5% of patients. Most patients develop non-specific symptoms such as weight loss, fever, diarrhoea, anorexia, asthenia, nausea and/or vomiting, or hypotension. Infection due to CMV is a major cause of bilateral adrenal destruction and is responsible for peripheral adrenal insufficiency in 3% of patients with AIDS [23]. Other opportunistic infections (Mycobacterium tuberculosis and MAI, Cryptococcus neoformans, Histoplasma capsulatum, Pneumocystis carinii and Toxoplasma gondii), neoplastic diseases (Kaposi’s sarcoma and lymphoma) and bilateral adrenal haemorrhage may also be responsible for reduced adrenal function [17].

Anti-adrenal antibodies have been detected in 45% of HIV-positive patients, probably reflecting non-specific activation of B-lymphocytes, but with no clinical impact [26,27].

Some drugs used in clinical practice in the management of HIV patients may also cause adrenal insufficiency, such as the antibiotic drug rifampicin or anti-fungal agents (Table 1).

Rifampicin is an antibiotic primarily used for mycobacterial infections, which accelerates the metabolism of cortisol via its inducing effect on cytochrome P450 enzymes, particularly CYP3A and CYP2C9 [28]. Rifampicin should be cautiously administered in patients with Addison’s disease, as it may favour acute adrenal insufficiency [29]. This potentially life-threatening side-effect can be prevented by routinely increasing the doses of hydrocortisone, by two or three, when starting treatment with
ADRENAL LESIONS

**UNILATERAL**

**Biological screening Tests**
- alkaline
- fasting glucose
- plasma or urinary metanephrines
- search for subclinical Cushing syndrome (Dexamethasone suppression test (1 mg), 24 hour urinary free cortisol, midnight plasmatic or salivary cortisol. plasma ACTH-8hrs.)

**Main causes**
- Specifically found in HIV patients:
  - **Parasitic Infections**: hydatid cyst(s)
- Common to the general population:
  - **Malignant Tumours**:
    - adenocortical carcinoma
    - leiomyosarcoma
  - **Benign Tumours**:
    - adenoma responsible for Cushing’s syndrome
    - Conn’s adenoma
    - pheochromocytoma
    - adenomatoid tumour
    - leiomyoma
  - **Intra-adrenal haematoma**

**BILATERAL**

**Biological screening Tests**
- alkaline
- fasting glucose
- plasma 17OH-progesterone
- plasma or urinary metanephrines
- search for subclinical Cushing syndrome (Dexamethasone suppression test (1 mg), 24 hour urinary free cortisol, midnight plasmatic or salivary cortisol. plasma ACTH-8hrs.)
- search for possible adrenal insufficiency: Synacthen stimulation test

**Main causes**
- Specifically found in HIV patients:
  - **Malignant Tumours**:
    - Kaposi’s sarcoma
    - non-Hodgkin’s lymphoma
  - **Opportunistic Infections**:
    - CMV, mycobacteria, Cryptococcus
- Common to the general population:
  - **Malignant Tumours**:
    - metastases
  - **Benign Tumours**:
    - bilateral adrenal Hyperplasia responsible for Cushing syndrome
    - primary hyperaldosteronism
    - pheochromocytoma
  - 21-hydroxylase deficiency
  - Bilateral adrenal haemorrhage

Fig. 1. Biological examination and aetiologies of adrenal incidentalomas in HIV-infected patients. Depending on the clinical context, other hormonal assays can be performed such as the search for hyperaldosteronism in cases of hypokalemia and/or hypertension, and adrenal androgen evaluation when adrenocortical carcinoma is suspected or in the presence of signs of hyperandrogenism.

rifampicin. Rifampicin may also acutely unmask a previously undiagnosed partial adrenal insufficiency. It is therefore preferable to assess the adrenocortical function by Synacthen test before initiating therapy with rifampicin.

Ketoconazole has long been used as an antifungal agent, especially to treat oesophageal candidiasis, common in immunosuppressed patients. It was withdrawn from the market in 2011 owing to its hepatic toxicity. Ketoconazole is a potent

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**Table 1**
Drugs commonly used for treatment of HIV patients and their impact on adrenocortical functions. Adrenal alterations often resolve after withdrawal of the offending agent.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Main indication</th>
<th>Adrenal impact</th>
<th>Pathophysiological mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitors and non-nucleoside reverse transcriptase inhibitors</td>
<td>Antiretroviral therapy</td>
<td>Pseudo-Cushing syndrome</td>
<td>Overexpression of 11β-hydroxysteroid dehydrogenase in adipose tissue Inflammation mediated by cytokines</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Treatment of mycobacterial infections</td>
<td>Acute adrenal insufficiency in patients with chronic adrenal failure</td>
<td>Accelerates metabolism of cortisol by cytochrome P450 enzyme induction</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Treatment of fungal infections (withdrawn from the market in 2011)</td>
<td>Adrenal insufficiency</td>
<td>Inhibits 11β-hydroxylase</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>Prevention or treatment of infections caused by <em>Pneumocystis jiroveci</em></td>
<td>Hyporeninism, hypoaldosteronism</td>
<td>Interstitial chronic nephritis (sulfonylurea) Sodium channel blockage in the distal part of the nephron (trimethoprim) Cortisol-like activity</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>Malnutrition, anorexia, cachexia</td>
<td>Cushing’s syndrome corticotropic insufficiency if sudden stop</td>
<td></td>
</tr>
</tbody>
</table>

inhibitor of adrenal steroidogenesis whose action inhibits 11-β-hydroxylase, an enzyme that catalyzes the final step of cortisol synthesis [30]. For this reason, ketoconazole is also used as a therapeutic alternative to pituitary gland surgery in Cushing’s disease. Like rifampicin, it may lead to adrenal insufficiency in predisposed HIV patients, most often in a dose-dependent manner [28].

Finally, it is important to notice that itraconazole, another frequently used anti-fungal agent, may be responsible for adrenal insufficiency after prolonged treatment, especially when combined with oral or inhaled corticosteroid therapy. This iatrogenic phenomenon involves potentiation of the inhibitory effect of exogenous corticosteroids on the hypothalamic-pituitary-adrenal axis via inhibition of the catalyzing CYP450 enzymes by itraconazole [31].

3.1.2. Corticotropic insufficiency

Different mechanisms can be responsible for corticotropic insufficiency in HIV patients: decreased pituitary and adrenal responses to corticotrophin releasing hormone (CRH) in advanced stages of AIDS [32], hypothalamic-pituitary necrosis or destruction caused by opportunistic infection agents (i.e. CMV, Mycobacterium tuberculosis, Toxoplasmosa gondii, Cryptococcus neoforms and Pneumocystis carinii) or tumours [33]. Anterior pituitary necrosis, probably related to a direct effect of the virus, has been observed in 10% of patients infected with HIV [34].

Finally, the cortisol response to the Synacten test may be below normal, reflecting partial adrenal insufficiency. This moderate decrease in glucocorticoid secretion can sometimes become clinically and biologically symptomatic during acute stress (due to trauma or infection), being responsible for arterial hypotension, severe asthma, hyperthermia or electrolyte abnormalities. Basal hypocortisolemia, even asymptomatic, should be treated by long-term supplementation with hydrocortisone. However, transient replacement therapy during limited periods of acute stress (surgery, pregnancy, severe infection etc.) may be sufficient in patients with partial adrenal insufficiency.

3.2. Excess of cortisol

Many HIV patients treated with antiretroviral drugs (particularly protease inhibitors and non-nucleoside reverse transcriptase inhibitors) (Table 1) were found to have several symptoms, including truncal obesity, buffalo neck, visceral adiposity, hypertension and diverse biological abnormalities (hyperglycaemia associated with insulin resistance, hypertriglyceridaemia…) mimicking Cushing’s syndrome. Plasma cortisol and urine free cortisol levels are sometimes high but the dexamethasone suppression tests show normal results in most studies. Despite the limited size of the published series, which produced only a low level of evidence, HIV is considered a possible aetiology of biological hypercortisolism, i.e. pseudo-Cushing syndrome [35–37].

Several phenomena can be potentially involved in the increase in cortisol levels in treated patients. Sutinen et al. [38] have raised the possibility of an overexpression of 11β-hydroxysteroid dehydrogenase (11βHSD) type 1 in adipose tissue, leading to increased cortisol synthesis from cortisone in adipocytes, even in the absence of elevated plasma cortisol levels. The mechanisms leading to overexpression of 11βHSD type 1 remain poorly understood, but the involvement of inflammation and cytokines is likely. In addition, the inhibitory action of protease inhibitors on the activity of the hepatic CYP3A4 enzyme, which results in a decreased cortisol metabolism, may favour elevation of cortisol levels [39].

Protease inhibitors are also able to slow down the catabolism of exogenous steroids via this mechanism. Thus, severe symptoms of hypercortisolism may occur when ritonavir, a powerful protease inhibitor, is combined with inhaled corticosteroids, particularly fluticasone [40]. It should also be noted that some patients treated with this drug association showed symptoms of adrenal insufficiency when the steroids were stopped, requiring temporary oral hydrocortisone supplementation.

In HIV-positive untreated patients, basal plasma cortisol levels were higher than those observed in healthy subjects, generally at moderately increased values [35,36]. Surprisingly, the plasma cortisol concentration did not sufficiently increase during the Synacten test despite high basal values [36]. Some studies have shown a significant negative correlation between CD4 cell count and plasma cortisol levels [41]. It was also observed that hypercortisolism may paradoxically be associated with unsuppressed levels of plasma ACTH but the results of the dexamethasone suppression test (1 mg) remained normal [35,42].

Several mechanisms may explain the increase in plasma cortisol levels in untreated HIV patients:

- the gp120 glycoprotein of the HIV seems to be able to activate the hypothalamic production and secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin [43];
- cytokines released during the inflammatory response to viral infection can stimulate the hypothalamic-pituitary-adrenal axis at different levels. In fact, interleukin (IL) 1β, but also IFN-α, IL-2, IL-6 and TNF-α, are able to increase CRH and ACTH productions [44], and IL-1β and IL-6 may directly stimulate the adrenal cortex (40,41);
- infectious stress is able to activate the corticotropi axis;
- HIV infection may be accompanied by a reduction in the cortisol catabolism [45] and an elevation in the circulating concentration of cortisol binding globulin (CBG) via an increase in its secretion and/or a decrease in its hepatic re-uptake [46]. This latter mechanism only affects the level of cortisol bound to CBG, which is taken into account by standard assays of plasma cortisol. It should therefore be recommended, in these patients, to rather use measurements of salivary cortisol, which reflects the free fraction of circulating cortisol.

Reciprocally, HIV-associated hypercortisolism contributes to the modifications in the cytokine pattern observed in advanced stages of the disease. In fact, cortisol decreases the ability of T lymphocytes to produce IL-2 and IFN-γ, and increase the production of IL-4 and IL-10 [4,47]. Cortisol thus slows down
the immune system activity, promoting viral replication. It is also involved in cachexia of AIDS patients by stimulating protein catabolism.

Some AIDS patients exhibit peripheral resistance to glucocorticoids, secondary to acquired defects in glucocorticoid receptor (GR) expression by lymphocytes. The density of GRs is increased, but their substrate binding affinity is reduced [48]. These patients have high plasma cortisol and ACTH levels with paradoxical clinical signs of adrenal insufficiency. Finally, long-term treatment with megestrol acetate, which is proposed in AIDS patients with cachexia for its orexigenic properties, is able to induce Cushing’s syndrome, via its cortisol-like intrinsic activity (Table 1). Abrupt discontinuation of megestrol acetate administration after prolonged use may also expose the patient to corticotrophic deficiency, due to previous inhibition of pituitary ACTH secretion.

4. HIV and mineralocorticoids

Patients with primary adrenal insufficiency exhibit mineralocorticoid deficiency, resulting in a low plasma aldosterone level associated with an increase in plasma renin concentration. Replacement therapy must then include fludrocortisone in addition to substitution with hydrocortisone.

In a longitudinal study of 26 HIV patients followed-up for 2 years [49], basal and ACTH-evoked aldosterone levels were found not significantly different to those measured in control subjects, i.e. seronegative for HIV. However, the aldosterone peak value was slightly decreased in the patients, an alteration which became more pronounced as the disease progressed.

In contrast, few cases of HIV (mostly untreated) patients with arterial hypertension, hypokalemia with elevated plasma aldosterone levels and a decrease in plasma renin activity have been described, therefore mimicking primary aldosteronism. One of the major pathophysiological hypotheses was that of a “renin-like” activity of the HIV aspartic protease, which would lead to aldosterone hypersecretion and subsequently hyporeninism [11].

Furthermore, a tendency towards hypoaldosteronism and hyporeninism has been noticed in HIV patients, although the published data are rather contradictory. At the onset of the HIV epidemic, prolonged and unexplained hyperkalemia were observed with lower plasma aldosterone and renin levels, and inadequate response to orthostatic and furosemide stimulation tests [50]. However, these data were challenged due to the concomitant use of cotrimoxazole (trimethoprim-sulfamethoxazole) in the patients studied. In fact, cotrimoxazole is the most widely used sulfonamide in the context of HIV infection, in particular for prevention and treatment of pulmonary infections caused by Pneumocystis jiroveci (Table 1). It is able to aggravate hyperkalemia, via a blocker effect of trimethoprim on the epithelial sodium channel (ENaC) expressed in the distal-convoluted tubule of the kidney, regardless of any action produced by aldosterone [51,52]. Consistently, trimethoprim behaves like a potassium-sparing diuretic in in vitro studies. Finally, sulfonamides can provoke chronic interstitial nephritis, a disease, which is known to be associated with hypoaldosteronism and hyporeninism.

5. HIV and adrenal androgens

The vast majority of clinical studies report a decrease in circulating levels of adrenal androgens during HIV infection, particularly dehydroepiandrosterone (DHEA), in both male and female patients [49,53]. It seems thus that synthesis of glucocorticoids is privileged at the detriment of adrenal androgens during the course of the disease.

In addition, it appears that DHEA level is correlated with the disease activity, including the rate of CD4+ T cells [47,54]. In vitro studies have also shown that T cells are capable of stimulating the production of DHEA sulphate (DHEA-S) in adrenocortical cells. This paracrine action requires direct contact between T cells and adrenocortical cells as observed in the zona reticularis of the adrenal cortex [55]. Adrenal androgen-secreting cells are the only adrenal cells, which express major histocompatibility complex class II antigens, which allows antigen presentation to T cells. It was shown in the same study that patients exposed to treatment with lymphocytotoxic drugs, like tacrolimus or cyclosporine, have significantly lower plasma levels of DHEA than control patients, although their glucocorticoid secretion remains normal. The defects in adrenal androgen secretion observed in patients treated with lymphocytotoxic compounds seem therefore to be similar to those observed in HIV patients and the molecular and cellular mechanisms involved are probably identical.

Promising studies had also suggested an in vitro inhibitory action of DHEA on viral replication [54]. In addition, DHEA was found to promote protein anabolism and stimulate the ability of T cells to produce IL-2 and IFN-γ, suggesting that the decrease in adrenal androgens may modulate the immune response and promote lipodystrophy and cachexia in patients with HIV [41]. Unfortunately, randomized controlled trials aimed at evaluating the potential benefit of DHEA administration in HIV patients have only shown a slight improvement in the quality of life and well being without any significant effect on markers of viral replication, such as CD4 rate or viral load, or on lipodystrophy.

6. Conclusion

Adrenal disease in HIV patients is frequently the consequence of the direct effects of the virus, opportunistic infections during the AIDS stage, and side-effects of antiretroviral treatment (which may be reversible following discontinuation of treatment). HIV infection can also be associated with malignant and benign adrenal tumours. Adrenal insufficiency is rare in this context but can be significant and require therapeutic care to avoid any clinical repercussions. It is thus necessary to explore the adrenal function in seropositive patients, who generally have few specific signs of adrenal insufficiency. In particular, adrenal testing is essential in the case of disseminated infection with CMV or mycobacteria, bilateral tumours and treatment with rifampicin or ketoconazole. Hydrocortisone replacement therapy is required in patients with an insufficient cortisol response.
to the Synacthen test. More exhaustive hormonal explorations must be conducted in the presence of a unilateral adrenal mass on CT scan and/or symptoms suggestive of adrenal hypersecretion.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


